

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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UNITED STATES OF AMERICA

3-1403  
*Invitation to  
Pay Additional  
fees due 4-19-03*  
INVITATION TO PAY ADDITIONAL FEES

PCT Article 17(3)(a) and Rule 40.1)

PCT

Date of mailing  
(day/month/year)

05/03/2003

Applicant's or agent's file reference  
689290-63

**PAYMENT DUE**

within 45 ~~XXXX~~ days  
from the above date of mailing

International application No.  
PCT/US 01/ 10838

International filing date  
(day/month/year)

30/05/2001

Applicant

AVALON PHARMACEUTICALS

1. This International Searching Authority

- (i) considers that there are 8447 (number of) inventions claimed in the international application covered by the claims indicated ~~XXXX~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~XXXX~~ on the extra sheet:

- (ii)  has carried out a partial international search (see Annex)  will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:  
**see extra sheet first invention**

- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited**, within the time limit indicated above, to pay the amount indicated below:

EUR 945,00	x	8446	=	EUR 7.981.470,00
Fee per additional invention		number of additional inventions		total amount of additional fees

Or, \_\_\_\_\_ x \_\_\_\_\_ = \_\_\_\_\_

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest**, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3.  Claim(s) Nos. further info have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority  
  
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Authorized officer

Marilú Masserut

## INVITATION TO PAY ADDITIONAL FEES

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-50 (partially)

Invention Number 1:

Sequence Identity Number 1, it being involved in a process for screening for an anti-neoplastic agent, it being involved in a process for determining the cancerous status of a test cell, it being involved in a process for determining a cancer initiating, facilitating or suppressing gene, it being involved in a process for treating cancer, it being involved in a process for determining functionally related genes, it being involved in a process for screening for an anti-neoplastic agent.

2. Claims: 1-50 (partially)

Invention Numbers 2 - 8447:

Idem for Sequence Identity Numbers 2 - 8447:

Sequence Identity Number 2 - 8447, them being involved in a process for screening for an anti-neoplastic agent, them being involved in a process for determining the cancerous status of a test cell, them being involved in a process for determining a cancer initiating, facilitating or suppressing gene, them being involved in a process for treating cancer, them being involved in a process for determining functionally related genes, it being involved in a process for screening for an anti-neoplastic agent.

The common element of the underlying application are Sequence Identities / genes differentially expressed in cancer. This common element though, namely Sequence Identities differentially expressed in cancer, is known from the prior art. L. Cheng et al, "Characterization of taxol-induced apoptosis and altered gene expression in human breast cancer cells", *Cellular Pharmacology* (1995), Volume 2, pages 249 - 257, identifies Taxol, a naturally occurring anti-neoplastic agent, capable of differentially inducing 12 different genes in human breast tumor, c.f. table 1 on page 253. Jochen Hess et al., "Application of differential cDNA screening techniques to the identification of unique gene expression in tumours and lymphocytes", *Current Opinion in Immunology* (1998), Volume 10, pages 125 - 130, identifies a multitude of genes, mainly involved in the cell-cycle regulation of proliferating cells, as being differentially expressed in cancer, c.f. page 127, paragraph on "Differential gene expression in tumorigenesis". Finally, S. Siavoshian et al., *Anticancer Research* (1999), Volume 19, pages 5361 - 5366, have identified differentially expressed sequences in lung carcinoma, c.f. page 5363, paragraph on Results.

In view of this prior art, the problem underlying the present application is considered to be the provision of further sequence identities / genes that are differentially expressed / regulated in cancer. Each of the specified sequence identities in the underlying

application represents an independent further solution to the aforementioned problem of the present application, discussed above, and in the view of the fact that differentially regulated / expressed genes / sequence identities are already known in the prior art, the ISA is of the opinion that there is no single inventive concept underlying the plurality of the claimed inventions conforming to the first said problem of the present application in the sense of Rule 13.1 PCT. Consequently, there is a lack of unity, and the different inventions, not belonging to a common inventive concept are formulated as the different subjects above pursuant to Article 17(3) (a) PCT. The ISA has searched the first mentioned subject above, namely the Sequence Identity Number 1 and its applications described in the first invention.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Although claims 17-21 and 32 - 39 are directed to a method of treatment of the human / animal body, the search has been carried out and based on the alleged effects of the compound/Sequence Identity.

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1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
 

see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE EBI 'Online! 3 August 1996 (1996-08-03) HILLIER, L. ET AL.: "ze23c03.s1 Soares fetal heart, H. sapiens cDNA clone, mRNA sequence;" retrieved from EMBL Database accession no. AA011199 XP002230815 the whole document --- 	1-50
Y	CHENG L ET AL: "Characterisations of taxol-induced apoptosis and altered gene expression in human breast cancer cells." CELLULAR PHARMACOLOGY, vol. 2, no. 6, 1995, pages 249-257, XP008013734 ISSN: 1351-3214 the whole document --- 	1-50
Y	WO 95 19369 A (UNIV VANDERBILT) 20 July 1995 (1995-07-20) the whole document --- 	1-50
Y	US 5 882 874 A (FISHER PAUL B) 16 March 1999 (1999-03-16) the whole document --- -/- 	1-50

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

**Annex to Form PCT/ISA/206  
COMMUNICATION RELATING TO THE RESULTS  
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No

PCT/US 01/10838

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>SIAVOSHIAN S ET AL: "Subtractive hybridization and differential screening identified two genes differentially expressed after induction of in vitro (atypical) terminal differentiation in the NSCLC-N6 cell line by a marine substance (bistramide K)."  <i>ANTICANCER RESEARCH.</i>, vol. 19, no. 6b, November 1999 (1999-11), pages 5361-5366, XP008013799  ISSN: 0250-7005  the whole document</p> <p>---</p>	1-50
Y	<p>KURDISTANI SIAVASH K ET AL: "Inhibition of tumor cell growth by RTP/rit42 and its responsiveness to p53 and DNA damage."  <i>CANCER RESEARCH</i>, vol. 58, no. 19, 1 October 1998 (1998-10-01), pages 4439-4444, XP001109678  ISSN: 0008-5472  the whole document</p> <p>---</p>	1-50
Y	<p>HESS J ET AL: "Application of differential cDNA screening techniques to the identification of unique gene expression in tumours and lymphocytes"  <i>CURRENT OPINION IN IMMUNOLOGY, CURRENT BIOLOGY LTD</i>, XX, vol. 10, no. 2, April 1998 (1998-04), pages 125-130, XP004327175  ISSN: 0952-7915  the whole document</p> <p>---</p>	1-50
Y	<p>VIETOR I ET AL: "In search of differentially expressed genes and proteins"  <i>BIOCHIMICA ET BIOPHYSICA ACTA. MOLECULAR CELL RESEARCH</i>, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 1359, no. 3, 12 December 1997 (1997-12-12), pages 187-199, XP004277797  ISSN: 0167-4889  the whole document</p> <p>---</p>	1-50
Y	<p>WO 99 50278 A (BEAUDRY GARY A ;GENZYME CORP (US); BERTELSEN ARTHUR H (US); MADDEN) 7 October 1999 (1999-10-07)  the whole document</p> <p>-----</p>	1-50

**Patent Family Annex**

Information on patent family members

International Application No

PCT/US 01/10838

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9519369	A	20-07-1995	US	5677125 A		14-10-1997
			AU	1831795 A		01-08-1995
			US	6342483 B1		29-01-2002
			WO	9519369 A1		20-07-1995
			AU	707348 B2		08-07-1999
			CA	2210396 A1		20-07-1995
			EP	0804453 A1		05-11-1997
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US 5882874	A	16-03-1999	AU	2881799 A		15-09-1999
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WO 9950278	A	07-10-1999	AU	3216899 A		18-10-1999
			CA	2323833 A1		07-10-1999
			EP	1066311 A1		10-01-2001
			JP	2002509707 T		02-04-2002
			WO	9950278 A1		07-10-1999
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